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CNS Late Effects After ALL Therapy in Childhood. Part I: Neuroradiological Findings in Long-Term Survivors of Childhood ALL—An Evaluation of the Interferences Between Morphology and Neuropsychological Performance

Holger Hertzberg, MD,[1] Walter J. Huk, MD,[2] Michael A. Ueberall, MD,[3] Thorsten Langer, MD,[1] Walburga Meier, PSYCHOL.,[4] Roland Dopfer, MD,[5] Martin Skalej, MD,[6] Herwig Lackner, MD,[7] Udo Bode, MD,[8] Gisela Janβen, MD,[9] Felix Zintl, MD,[10] and Jörn D. Beck, MD,[1]* for the German Late Effects Working Group

The effect of cranial irradiation on possible therapy-induced morphological central nervous system (CNS) side effects of children cured from acute lymphoblastic leukemia (ALL) is controversially discussed.

In a retrospective multicenter study, 118 former ALL patients in first continous remission were investigated using cranial computerised tomography (CCT) or magnetic resonance imaging (MRI) scans to evaluate CNS related impairments. Corresponding to the different kinds of CNS prophylaxis, the patient sample was divided: group A (n = 39) receiving intrathecal methotrexate (ITMTX) and systemical medium-high-dose methotrexate (SMHDMTX), group B (n = 41) cranial irradiated (in mean 16.8 Gy) and administering ITMTX and SMHDMTX, group C (n = 38) irradiated (in mean 17.1 Gy) and getting ITMTX. Pathologic scans showed atrophy, leukoencephalopathy, calcifications or grey matter changes. These findings were compared with the neuropsychological test results.

Abnormal MRI or CCT scans were found in 61/118 patients (51.7%). Fifteen belonged to group A (38.5%), 23 to B (56.1%) and 23 to C (60.5%). Patients with definite CNS changes show reduced neuropsychological test results. The prevalence of brain alterations seems to appear twice increased after lengthening the posttherapeutic interval in irradiated patients as in nonirradiated patients. Irradiated patients with an age younger than 2 years at diagnosis may show a lower prevalence for developing CNS alterations. CNS alterations are not sex-related.

Children treated with cranial irradiation in combination with SMHDMTX and/or ITMTX were at greater risk of developing morphological brain alterations than patients with chemotherapy alone. These alterations are partly correlated with reduced neuropsychological performances and seem to stay with a longer posttherapeutic interval. Med. Pediatr. Oncol. 28: 387–400, 1997.

Key words: acute lymphoblastic leukemia; brain alterations; CNS prophylaxis; cranial irradiation; late effects; neuroradiology

INTRODUCTION

In the past two decades, the treatment of acute lymphoblastic leukemia (ALL) has improved the overall survival rates to almost 80% in the current Berlin-Frankfurt-Münster (BFM) study [1]. One reason for this success was the establishment of an effective central nervous system (CNS) prophylaxis to prevent CNS leukemia [2,3]. In the 1970s, large clinical trials confirmed that the prophylactic cranial irradiation (CI), either on its own or combined with intrathecal chemotherapy, increased the number of survivors of ALL in childhood [4–6]. Nowadays, increasing attention is focused on the possible late effects of such an effective but eventually harmful prophylaxis in a growing sample of survivors. A large number of studies with often contradicting results about the neuropsychological, neurophysiological and neuroradiological effects of anti-leukemic treatment has been carried out [7–9]. In several neuroradiological examinations, anatomical CNS changes were predominantly observed in irradiated patients [10,11]. Irradiated patients presented more frequent focal white matter necrosis, brain atrophy, calcifications and grey matter changes in

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The institutions and investigators participating in the CNS Late Effects Working Group are listed in the Appendix.

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[1]From the Department of Pediatric Immunology and Oncology, University Hospital for Children and Adolescents, Erlangen, Germany; [2]Department of Neuroradiology, University Erlangen-Nürnberg, Germany; [3]Neuropediatric Department, University Hospital for Children and Adolescents, Erlangen, Germany; [4]Hospital for Psychosomatic Diseases, Bad Wildungen, Germany; [5]Department of Pediatric Oncology, Childrens Hospital, University of Tübingen, Germany; [6]Department of Neuroradiology, University of Tübingen, Germany; [7]Department of Pediatric Oncology, Childrens Hospital, University of Graz, Austria; [8]Department of Pediatric Oncology, Childrens Hospital, University of Bonn, Germany; [9]Department of Pediatric Oncology, Childrens Hospital, University of Düsseldorf, Germany; [10]Department of Pediatric Oncology Childrens Hospital, University of Jena, Germany.

*Correspondence to: Dr. J.D. Beck, Department of Pediatric Immunology and Oncology, University Hospital for Children & Adolescents, Loschgestraβe 15, 91054 Erlangen, Germany.

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radiological examinations. On the other hand, there are studies which report no significant differences between the irradiated and nonirradiated patients [12–15].

Summing up the results of these studies, the combined use of CI and chemotherapy appears to induce more morphological CNS alterations than therapy modalities without irradiation. This may be valid, especially for those combinations in which intrathecal methotrexate (IT-MTX) is employed during or after the CI. However, considering the published data, there are methodological shortcomings: many studies involved only a small number of patients and the evaluated population differed with regard to the post-therapeutic interval, the risk scores and therapy. Despite this variability, they were still frequently investigated as one group. Since the 1980s most of the children have been prophylactically irradiated with a maximum dose of only 18 Gy or were treated with systemic medium-high-dose methotrexate (SMHDMTX) and ITMTX without CI. However, the published studies often investigated children receiving CI with 24 Gy [11,16,17].

To clarify the points mentioned above, we initiated in 1992 a multicenter study in Germany and Austria to evaluate CNS late effects after ALL therapy in childhood [18–20]; this study group is part of a working group ''late effects'' founded by the Gesellschaft für Pädiatrische Onkologie und Hämatologie to study late effects in former pediatrics cancer patients [21]. A representative number of former ALL patients who had been enrolled in comparable therapy studies in 1981–1986 were examined by a standard investigation program.

Therefore it was our intention to elucidate the following hypotheses: (1) does a therapy regimen using cranial irradiation with a maximum dose of 18 Gy induce more morphological CNS abnormalities than a regimen without irradiation? and (2) Are such morphological abnormalities correlated with neuropsychological impairments? This paper presents data concerning the morphological variation of brain alterations and its correlation to neuropsychological performance observed in this study population.

MATERIALS AND METHODS

Patient Sample

The follow-up trial was carried out according to the provisions of the Declaration of Helsinki (1975, revised in 1983). After the consent of the Medical Ethics Committee of the University Erlangen-Nürnberg (Germany), a total of 163 ALL patients who had been treated in 11 hospitals in Germany and Austria were entered in our retrospective study between June 1992 and December 1994. Written informed consent for participation was obtained from the patients or their parents. From the total of 163 patients, 21 withdrew due to violations of study inclusion and exclusion criteria (see below). In a further group of 24 patients, neither CCT nor MRI scans were performed. The available CCT or MRI scans described in this report are obtained from 118 (72%) patients. Demographical and clinical data as well as the splitting up into our three treatment groups (i.e., A, B and C) of the excluded 45 (28%) patients did not differ in a relevant way from those 118 described here. These had stopped receiving therapy for more than 7.2 years in mean (range: 4.5–10.6 years). The mean age at the time of diagnosis was 5.8 years (range: 0.3–16.1 years), the mean age of investigation was 14.7 years (range: 8.0–27.8 years) and the ratio of male:female was 58:60.

Eligibility Requirements

All patients were treated according to the protocols of the BFM study group BFM-81/83 [22,23] or to the corresponding COALL protocols COALL-80/82 [24]. Patients with a standard/low or middle risk (risk factor [RF] < 1.7) without CNS involvement and a first continuous remission were enrolled. They had to be older than 6 years at the time of investigation, had visited or were visiting a German school and were fluent in German.

Exclusion Criteria

Selected patients had neither any evidence of initial CNS leukemia nor had they developed a CNS relapse or a secondary malignancy. The patients should not have had a meningeal or encephalitic infection before the investigation or been suffering from the effect of a perinatal hypoxia. In addition, a preexistent neurological and/or psychiatric disease excluded patients from participation. No constitutional numeric or structural chromosomal aberrations should be detected.

Treatment

All patients had been consecutively enrolled into BFM/COALL protocols [22–24] and were assigned to different prophylactic CNS treatments. First we describe the CNS relapse incidence of the different treatment branches. The analysis of the BFM studies was performed in June 1995 (M. Schrappe, BFM study center, personal communication). The COALL studies were analysed in May 1996 (G.E. Janka-Schaub, COALL study center, personal communication). The following isolated and combined CNS relapse rates were documented: BFM 81 SR-A ($n = 184$): 6 (3.3%) relapses with CNS involvement (RCNS); BFM 81 SR-B ($n = 178$): 25 (14.1%) RCNS; BFM 81 MR ($n = 204$): 19 (9.3%) RCNS; BFM 83 SR-L1 ($n = 104$): 14 (13.5%) RCNS; BFM 83 SR-L2 ($n = 95$): 6 (6.3%) RCNS; BFM 83 SR-H1 ($n = 86$): 4 (4.7%) RCNS; BFM 83 SR-H2 ($n = 105$): 3 (2.9%) RCNS; BFM 83 MR ($n = 230$): 22 (9.7%) RCNS; COALL 82 LR ($n = 66$): 8 (12.1%)

RCNS. Patients with CNS relapses were not included in our study recognisable in the eligibility requirements and exclusion criteria.

For analysis, all treatment branches were divided into three treatment groups disregarding minor differences between the protocol branches and their influence on CNS prophylaxis. Group A included the treatment branches of the BFM-protocols BFM-81/SR-B, BFM-83/SR-L1/2 and COALL-protocol 82/LR, group B the branches BFM-83/SR-H1/2 and BFM-83/MR and group C the branches BFM-81/SR-A and BFM-81/MR (Table I). Group A (n = 39) received only SMHDMTX (cumulative dose 2,000 mg/m^2 body surface [BS] in four infusions) and ITMTX (cumulative mean dose 81 mg (range: 48–168 mg age-dependently) in 6 to 8 injections) for CNS prophylaxis. Group B (n = 41) was treated with CI with a dose ranging age-dependently from 12 to 18 Gy (in mean 16.8 Gy) combined with SMHDMTX (cumulative dose 2,000 mg/m^2 BS in four infusions) and ITMTX (cumulative mean dose 93 mg (range 40–108 mg dependent on age in eight injections). CI was performed after the administration of MHDMTX and ITMTX. Group C (n = 38) was treated with CI, with a dose ranging age-dependently from 12 to 18 Gy (in mean 17.1 Gy) combined with ITMTX during (four injections) and after (two injections) the CI in a cumulative mean dose of 68 mg (range 40–84 mg age-dependently). No SMHDMTX was given in this group (Table I).

Relevant data with respect to initial clinical features, illness and treatment parameters of the investigated subjects are summarised in Table I.

Study Design

An extensive examination which included the patient's case history and social background was carried out to estimate the social, psychological and educational factors. The neurological examination was performed using the Touwen pattern [25]. Neurophysiological investigations with electroencephalogram (EEG), visual evoked potentials (VEP) and event-related potentials (ERP) were carried out whenever available. MRI or CCT scans were obtained for the neuroradiological examination. For the neuropsychological tests, the Wechsler scales (WISC-R, WAIS-R) [26,27] and the Culture Fair Test (CFT) by Cattel for intelligence measures [28,29], the Recurring Figures Test for memory functioning [30–32] and the d2-Concentration Test [33] were performed. In addition to the Wechsler scales, three further measures were taken which reflect the main factors of ability as defined by Kaufman [34] and converted in standard deviation quotients with formulas by Tellegen and Briggs [35] and Sattler [36]: verbal comprehension (VC), dependent on Wechsler Scale subtests ''information,'' ''similarities,'' ''vocabulary'' and ''comprehension''; perceptual organisation (PO), calculated from ''picture completion,'' ''picture arrangement,'' ''block design,'' and ''object assembly'' subtests; and the freedom from distractibility (FD), based on subtests ''digit-span,'' ''arithmetics,'' and ''coding.'' The results of each of these sections were evaluated by an experienced investigator (neurologist: K. Berger-Jones, neurophysiologist: R. Korinthenberg, neuroradiologist: W.J. Huk, psychologist: W. Meier) who had no knowledge of the patient's medical history and the results of our study.

Neuroradiological Examination

After informed consent had been obtained from the patients or their parents, MRI scans, CCT scans or both were performed. Overall, 49 CCT scans and 78 MRI scans have been done. In nine patients, both scans have been available. In group A, 13 CCT, 21 MRI and 5 CCT and MRI scans were obtained. Group B enrolled 13 patients who were examined with CCT, 27 with MRI and three who had both. Sixteen CCT scans and 21 MRI scans were obtained in group C; an additional patient of group C received a CCT and a MRI scan. Serial axial images were obtained at a slice thickness of 4 / 8 mm below / above the cerebellar tentorium. The CCT scans were performed with soft tissue contrast. A Gantry angulation of −20° in relation to the meato-orbital line to prevent ocular irradiation was used when CCT scans were performed. In MRI scans, T_2-weighted and proton density images were analyzed. No contrast medium was applied. The qualitative assessment of MRI and CCT scans was performed by W.J. Huk, who had no prior information about the individual histories of the presented cases. Pathologic criteria were: widening of the sulci (WS) or ventricles (WV), findings believed to indicate cerebral atrophy; low-density areas (LDA) in CCT scans or hyperintense areas in MRI, respectively, in the white matter, suspect for leukoencephalopathy; high-density (HDA) in CCT scans or hypointense areas in MRI, respectively, and calcifications (CALC) in CCT scans as indicator for calcified focal brain necrosis; grey matter changes (GMC) as a further possible sign for brain necrosis.

MRI and CCT scans were classified as normal if they showed no evidence of any of these findings and no other morphological abnormality. In the following text, both low-density areas in the CCT scans and hyperintense areas in MRI are abbreviated with ''LDA'' and conversely ''HDA'' for high-density areas in the CCT scans and hypointense areas in the MRI scans.

Statistical Analysis

First we looked for a difference to show morphological CNS abnormalities between the nonirradiated group A and the irradiated patients (group B + group C). Second, we analysed for a difference between the both irradiated groups which obtained as additionally CNS

TABLE I. Sample Description†

	Overall Mean ± S.D.	Treatment groups: Group A[a] Mean ± S.D.	Group B[b] Mean ± S.D.	Group C[c] Mean ± S.D.	*P*-value* (A/B/C)
Demographic data					
Number	118.00	39.00	41.00	38.00	
Age at diagnosis (yrs.)	5.77 ± 4.08	6.72 ± 4.55	5.16 ± 3.66	5.46 ± 3.93	0.200
Age at investigation (yrs.)	14.72 ± 4.40	15.60 ± 4.88	12.74 ± 3.60	15.95 ± 4.02	0.001
Post-therapeutic interval (yrs.)	7.17 ± 1.77	7.05 ± 1.73	5.76 ± 1.00	8.72 ± 1.03	0.001
Male-to-female ratio	58/60	19/20	22/19	17/21	0.730
Clinical data at diagnosis					
Hb[d] (mg/dl)	7.76 ± 2.55	6.99 ± 2.05	8.19 ± 2.64	8.20 ± 2.85	0.080
Platelets (cells/μl)	73235 ± 73409	79771 ± 80874	65352 ± 58788	74586 ± 80761	0.720
WBC[e] (cells/μl)	20645 ± 30910	6737 ± 8582	27723 ± 38903	27042 ± 32495	0.003
Blasts (cells/μl)	14791 ± 28145	3212 ± 8482	20451 ± 34197	20717 ± 31065	0.006
Blasts (%)	43.04 ± 32.14	25.08 ± 27.33	54.44 ± 29.22	49.18 ± 32.47	0.001
Liver (cm)	3.29 ± 2.48	2.11 ± 2.05	3.90 ± 2.51	3.90 ± 2.47	0.002
Spleen (cm)	2.39 ± 2.66	0.64 ± 1.25	3.41 ± 2.90	3.13 ± 2.60	0.001
Risk factor[f]	0.95 ± 0.37	0.66 ± 0.22	1.09 ± 0.37	1.11 ± 0.31	0.001
Morphology					
FAB[g] L1 (%)	64.70	76.90	55.60	65.00	
FAB L1–2 (%)	17.60	7.70	33.30	10.00	0.240
FAB L2 (%)	17.60	15.40	11.10	25.00	
Methods of therapy					
Radiotherapy (%)	66.7	—	100	100	
Mean total dose (Gy)[h]	11.26 ± 8.30	—	16.75 ± 2.33	17.05 ± 3.13	0.001
Mean dose/fraction (Gy)	1.11 ± 0.95	—	1.87 ± 0.47	1.71 ± 0.45	0.001
Energy (MV)[i]	1.77 ± 2.35	—	3.16 ± 1.56	3.65 ± 2.96	0.001
Cumulative ITMTX[j] (mg)	80.58 ± 21.33	80.56 ± 16.82	92.70 ± 25.42	67.49 ± 10.72	0.001
ITMTX applications (No.)	6–8	6–8	8 before CI[l]	4 during, 2 after CI	
Cumulative SMHDMTX[k] (mg/m^2)	1338 ± 9421	2000 ± 0	1963 ± 237	—	0.001
SMHDMTX applications (no.)	0–4	4	4	—	
Duration (months)	21.75 ± 2.90	22 ± 2.87	21.92 ± 2.85	21.32 ± 3.02	0.53
Treatment branches					
BFM[m] branches (year/branch)		81/SR-B 83/SR-L 1/2	83/SR-H 1/2 83/MR	81/SR-A 81/MR	
COALL[n] branches (year/branch)		82/LR			

†Demographical/clinical data and treatment parameters overall and in the different treatment groups.
[a]Group A, nonirradiated subjects who received only intrathecal and intravenous methotrexate for central nervous system prophylaxis.
[b]Group B, irradiated subjects who received cranial irradiation before intrathecal and intravenous methotrexate applications.
[c]Group C, irradiated subjects who were treated with intrathecal methotrexate applications during and after cranial irradiation.
[d]Hb, hemoglobin.
[e]WBC, white blood cell count.
[f]Risk factor, tumor mass index calculated as follows: 0.2 * log (peripher blasts/μl + 1) + 0.06 * liver size under the costal arch [cm] + 0.04 * spleen size under the costal arch [cm].
[g]FAB, French-American-British-Group classification of leukemias.
[h]Gy, gray.
[i]MV, megavolt.
[j]ITMTX, intrathecal methotrexate.
[k]SMHDMTX, systemic medium-high dose methotrexate.
[l]CI, cranial irradiation.
[m]BFM, The German Berlin-Frankfurt-Münster therapy study group for acute lymphoblastic leukemia.
[n]COALL, The German Cooperative study group for acute lymphoblastic leukemia.
*The obtained *P*-values are from a three-way Chi-square test or an one-way ANOVA between Groups A, B and C.

therapy two different kinds of MTX regimens (Table I). The further analysis investigated the correlations between morphological changes and psychological impairments. Statistical analysis was performed with two- or three-way Chi-square test to evaluate the relationship between categorial variables, Mann-Whitney nonparametric rank test, two-sided t-test and a one-way ANOVA for independent samples, using the procedures of the Su-

TABLE II. MRI/CCT Findings†

Treatment group (n = 118)	Group A[a] (n = 39)		Group B[b] (n = 41)		Group C[c] (n = 38)		Group B + C[d] (n = 79)		*P*-value* (A/B + C)
	n	%	n	%	n	%	n	%	
Abnormal MRI[e]/CCT[f] scans	15	38.5	23	56.1	23	60.5	46	58.2	0.043
One abnormal finding	11	28.2	11	26.8	9	23.7	20	25.3	0.540
2–4 abnormal findings	4	10.3	12	29.3	14	36.8	26	32.9	0.006
Widening of the sulci (WS)	8	20.5	10	24.4	14	36.8	24	30.4	0.257
Widening of the ventricles (WV)	9	23.1	10	24.4	14	36.8	24	30.4	0.406
High-density areas (HDA)	1	2.6	5	12.2	3	7.9	8	10.1	0.145
Low-density areas (LDA)	1	2.6	11	26.8	9	23.7	20	25.3	0.001
Grey matter changes (GMC)	0	0	2	4.9	0	0	2	2.5	0.446
WS + WV	3	7.7	5	12.2	10	26.3	15	19.0	0.088
Any widening + LDA	0	0	5	12.2	5	13.2	10	12.7	0.015
Any widening − LDA	14	35.9	10	24.3	13	34.2	23	29.1	0.294
Calcifications (CALC) detected in CCT scans (n = 49)	(n = 18)		(n = 14)		(n = 17)		(n = 31)		
	0	0	3	21.4	1	5.9	4	12.9	0.149

†Magnetic resonance imaging and cranial computerised tomography findings in the different treatment groups.
[a]Group A, nonirradiated subjects who received only intrathecal and intravenous methotrexate for central nervous system prophylaxis.
[b]Group B, irradiated subjects who received cranial irradiation before intrathecal and intravenous methotrexate applications.
[c]Group C, irradiated subjects who were treated with intrathecal methotrexate applications during and after cranial irradiation.
[d]Group B+C, combined group (Group B and Group C) who received all a cranial irradiation as part of the central nervous system prophylaxis.
[e]MRI, magnetic resonance imaging.
[f]CCT, cranial computerised tomography.
*The obtained *P*-values are from the Chi-square test between Group A and Group B + C.

perior Performing Software System for Windows (SPSS-WIN), Version 5.02 (Norusis 1993).

RESULTS

The results of the MRI and CCT investigations are reported in Table II and Figures 1–5. The significant correlations of the MRI/CCT alterations and the psychological investigations are given in a summarised form in Table III. Percentages given are within group percentages. Abnormal MRI/CCT scans, defined as one or more findings, were found in 61 of 118 patients investigated (51.7%). Fifteen of 39 of those belonged to group A (38.5%), i.e., the group without CI for CNS prophylaxis. Twenty-three of 41 of them were part of group B (56.1%), i.e., the group which received chemotherapy before CI, and 23/38 counted to group C (60.5%), i.e., the group who were treated with ITMTX during or after CI for CNS prophylaxis (Table II, Fig. 2). Thus, 75.4% of all abnormal MRI/CCT scans are within the irradiated groups, finding a significant difference between group A and group B + C ($P = 0.043$).

Table II shows the number and kinds of abnormal findings in groups A, B and C. The distribution of only one abnormal MRI/CCT finding was approximately equal between the three groups: in all groups about 24–28% of the patients demonstrate only one abnormality. The majority of irradiated patients showed more changes regarding the appearance of more than one abnormality: two or more findings were seen in group A in 4/39 (10.3%), in group B in 12/41 (29.3%) and in group C in 14/38 (36.8%). Between group A and group B + C a significant difference was observed ($P = 0.006$).

Focusing the interest on the specific pathologic criteria investigated (Table II, Fig. 1), cases with LDA were found in group A in 1/39 (2.6%), in group B in 11/41 (26.8%) and in group C in 9/38 (23.7%). The appearance of LDA was significantly different between group A and group B + C ($P = 0.002$). The appearance of calcifications, only definitely detectable in the performed CCT scans (n = 49), was seen in group B in 3/14 cases (21.4%) and group C in 1/17 cases (5.9%).

This observation as well as the other observations of single findings are insignificant, but showed a tendency to more abnormal MRI/CCT scans in the groups with CI (Table II and Figs. 1,2). Regarding the simultaneous appearance of WS and WV, indicating both brain atrophy, the groups with CI showed more combined widenings. Although group C showed combined widenings in 10/38 of the cases (26.3%), group B in 5/41 (12.2%) and group A only in 3/39 (7.7%), there was no significant difference between group A and group B + C ($P = 0.088$).

When considering the combination of any widening (WS or WV) with the finding of LDA, no patient from group A demonstrated such a combination in contrast to group B (5/41, 12.2%) and group C (5/38, 13.2%). There were significant differences between group A and group B + C ($P = 0.015$) (Table II, Fig. 2). As Table II shows, the appearance of any widening without LDA is distributed almost equally amongst the three groups (group A: 14/39 (35.9%), group B: 10/41 (24.3%) and group C: 13/38 (34.2%)).

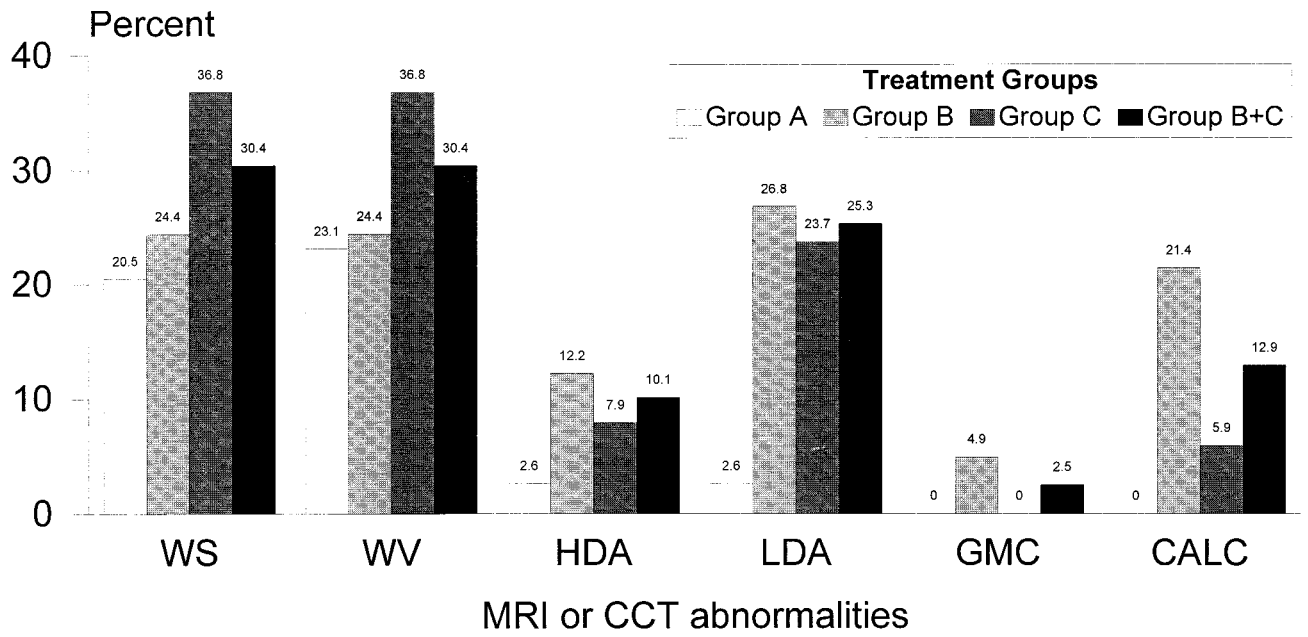

Fig. 1. MRI or CCT findings. MRI, magnetic resonance imaging; CCT, cranial computerised tomogram; WS, widening of the sulci; WV, widening of the ventricles; HDA, high-density area in CCT scans (and hypointense area in MRI scans); LDA, low-density area in CCT scans (and hyperintense area in MRI scans); GMC, grey matter changes; CALC, calcifications (only CCT); Group A, nonirradiated subjects who received only intrathecal and intravenous methotrexate for central nervous system prophylaxis; Group B, irradiated subjects who received cranial irradiation before intrathecal and intravenous methotrexate applications; Group C, irradiated subjects who were treated with intrathecal methotrexate applications during and after cranial irradiation; Group B+C, combined group (Group B and Group C) who received all a cranial irradiation (8–18 Gy) as part of the central nervous system prophylaxis. Data show the different kinds of abnormal findings in percent of the total treatment group (i.e., A, B, C or B+C).

Calcifications (n = 4) appeared in three patients with LDA and in one patient with HDA, all four irradiated. No calcifications were detected within the groups who had a widening of the cerebro-spinal fluid spaces. Between the two irradiated groups (group B and group C) we found no significant difference in all investigations done above with group A and group B + C. Although there are significant differences between all three groups regarding the age at investigation ($P = 0.001$) and the post-therapeutic interval ($P = 0.001$; Table I), these findings do not have any influence on the observations of abnormal MRI/CCT findings between these groups as the performed discriminant analysis have shown. The other significant differences of the clinical and therapy data (Table I) reflect the different treatment groups to which the patients belong to.

Looking at the age-dependent frequency of the total number of abnormal MRI/CCT scans, we note that the irradiated patients are at a higher risk to present abnormal MRI/CCT scans in all age groups than the non irradiated (data not shown). Irradiated patients who were aged up to 2 years at the time of diagnosis have a prevalence of 30%, whereas all other age groups up to older than 6 have a prevalence above 50% of abnormal MRI/CCT findings. The highest prevalences are in the groups older than 4 and up to 5 (71.4%) and older than 5 and up to 6 (83.3%; Fig. 3) in regard of the low group size (10–18 patients per group). The irradiation dose did not differ in the younger than 2 age group from those who were older (15.9 Gy vs. 17.3 Gy in mean). The age-related distribution of any widening among the irradiated groups shows that younger children in the age groups up to 4 years show in 13/41 (31.7%) patients this abnormality, whereas the children who are 4 years or older at diagnosis, show this finding in 20/38 (52.6%) of the cases (Fig. 4).

Looking at the distribution of age at diagnosis of those patients who show low-density areas in CCT (or hyperintense areas in MRI), we recognize that 15/21 (71.4%) of patients with LDA are older than 2 and younger than 5 years (Fig. 4). These are 39.5% of all irradiated patients in these age groups (n = 38). Of those who were younger than 2 (n = 12) only one patient (8,3%) present a low-density area. This patient was an irradiated one (1/10, 14.3%). No low-density areas are detected in patients without irradiation (n = 18).

Comparisons between the post-therapeutic interval and the frequency of abnormal MRI/CCT scans show that within the irradiated groups the number of abnormal MRI/CCT findings reaches a higher level with a post-therapeutic interval greater than 7 years than in the non-irradiated group as Figure 5 describes (53.3–66.7% vs. 28.6–40.6%), but this is statistically insignificant.

Regarding a difference in the psychological data between the groups with normal and abnormal MRI/CCT scans, we can state that there is a tendency to score lower

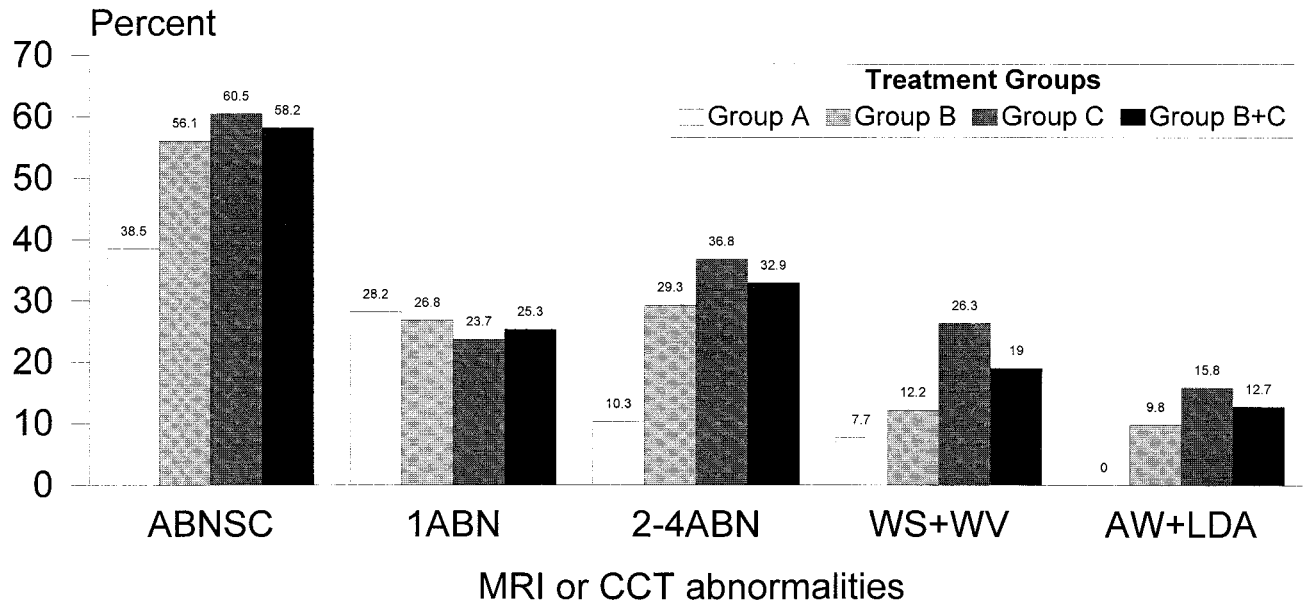

Fig. 2. Distribution and combination of abnormal findings. ABNSC, overall abnormal MRI/CCT scans; 1 ABN, only one abnormality found; 2–4 ABN, 2–4 abnormalities found; WS + WV, widening of the sulci and of the ventricles; AW + LDA, any widening (widening of the sulci or of the ventricles) and low-density area in CCT scans (hyperintense area in MRI scans); Group A, nonirradiated subjects who received only intrathecal and intravenous methotrexate for central nervous system prophylaxis; Group B, irradiated subjects who received cranial irradiation before intrathecal and intravenous methotrexate applications; Group C, irradiated subjects who were treated with intrathecal methotrexate applications during and after cranial irradiation; Group B+C, combined group (Group B and Group C) who received all a cranial irradiation (8–18 Gy) as part of the central nervous system prophylaxis. Data show the number of abnormal findings and the combination of different findings expressed in percent of the total treatment group (i.e., A, B, C or B+C).

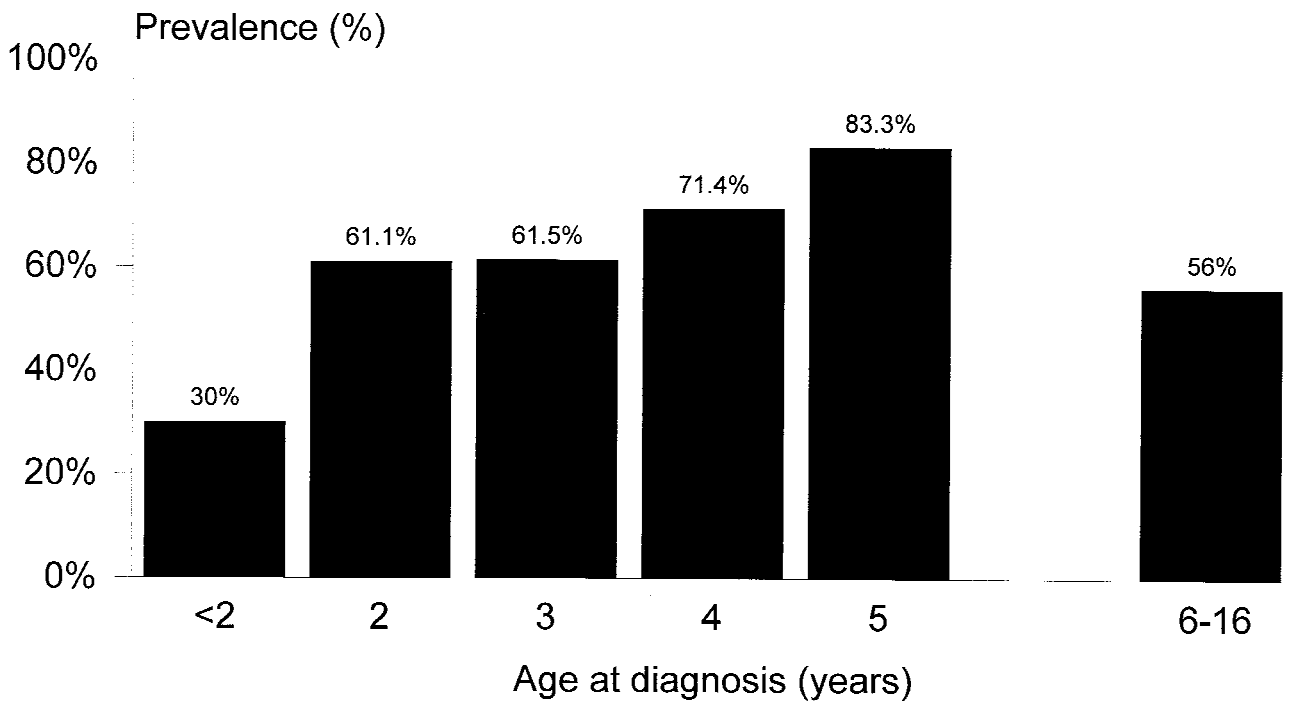

Fig. 3. Prevalence of abnormal MRI or CCT scans in the irradiated groups. MRI, magnet resonance imaging; CCT, cranial computerised tomogram. Bars show the prevalence of abnormal MRI/CCT scans in the irradiated (8–18 Gy) groups (Group B+C), regarding the different age groups at time of diagnosis.

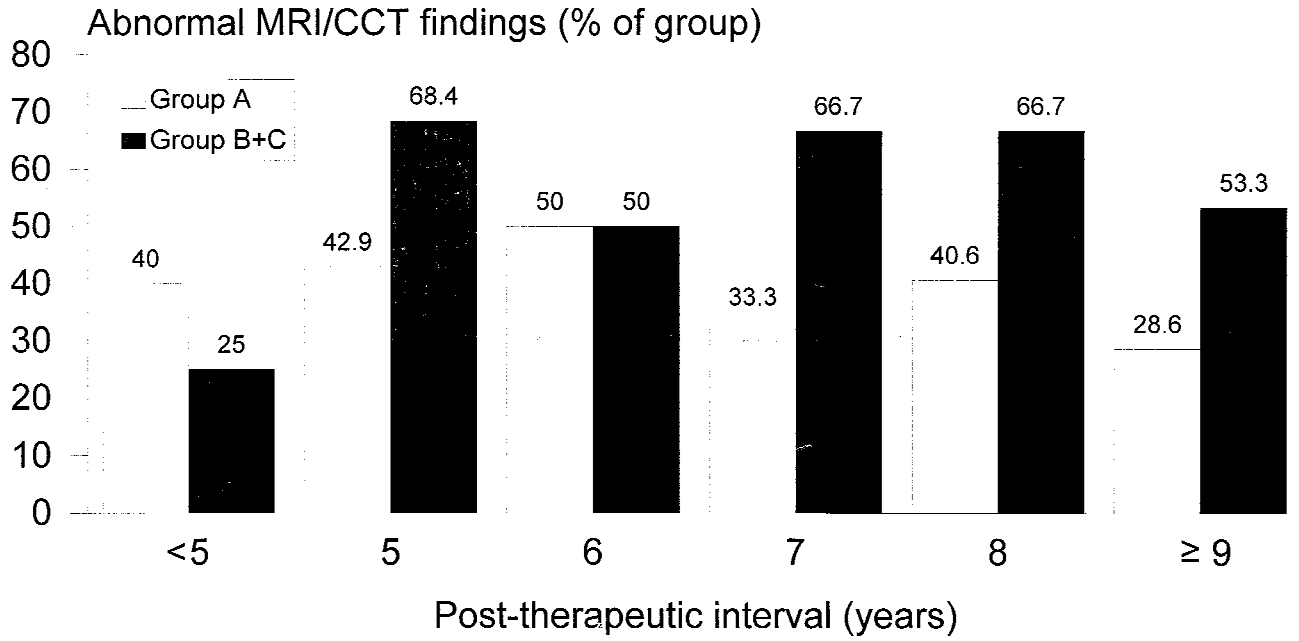

Fig. 4. Distribution of any widening and low density areas of irradiated patients in relation to age at diagnosis. Bars show the number of findings within the irradiated patients in percent. The number of the irradiated patients per age group is given below the age.

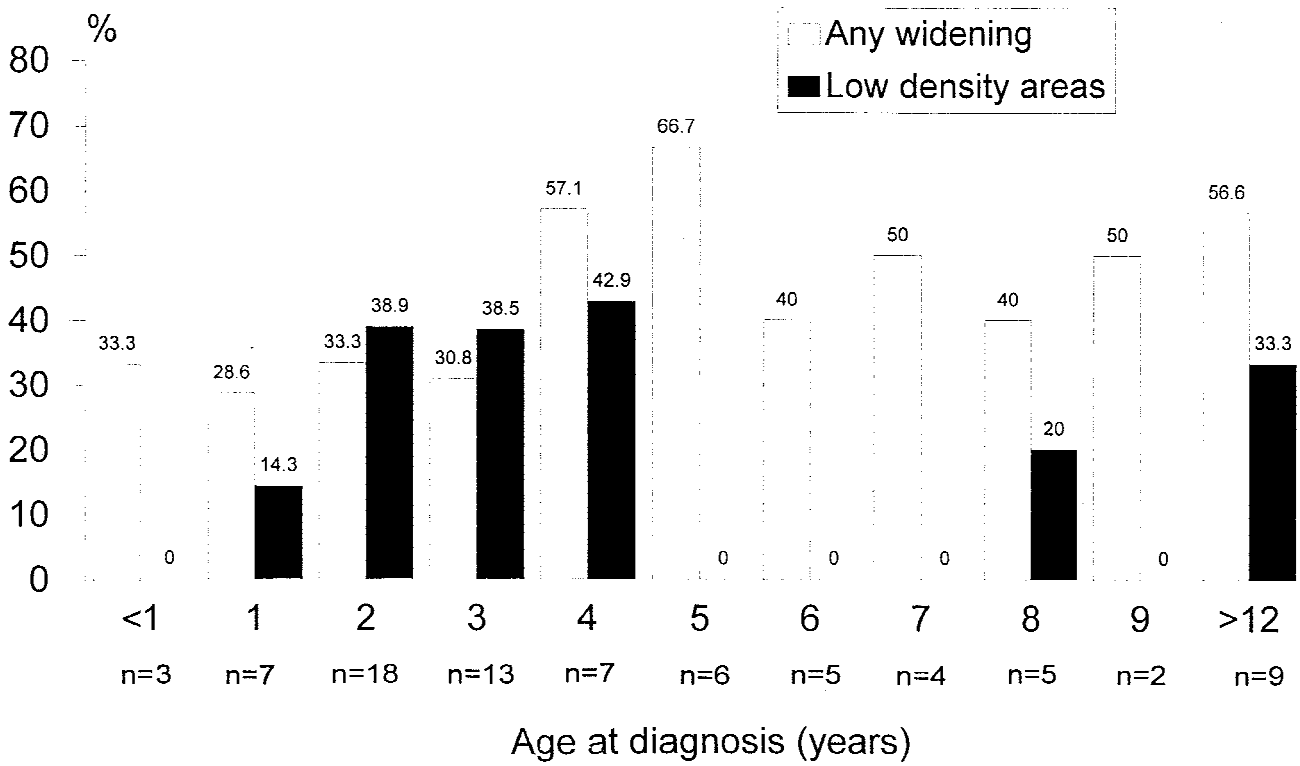

Fig. 5. Abnormal MRI/CCT findings of the different treatment groups in relation to the post-therapeutic interval. MRI, magnetic resonance imaging; CCT, cranial computerised tomogram; Group A, nonirradiated subjects who received only intrathecal and intravenous methotrexate for central nervous system prophylaxis; Group B+C, combined group (Group B and Group C) who received all a cranial irradiation (8–18 Gy) as part of the central nervous system prophylaxis. Bars show the number of abnormal MRI/CCT findings of the different treatment groups in percent regarding to the different post-therapeutic intervals.

TABLE III. Correlations Between MRI/CCT Subitem Findings and Psychological Test Results

Psychological tests	Mean ± S.D.	P-value*	Mean ± S.D.	Mean value of norm population ± S.D.
	No finding (n = 55)		Any finding (n = 60)	
d2-Test (%)[f]	56.95 ± 30.31	0.042	45.40 ± 28.89	50 ± 34
	No LDA[a] (n = 94)		LDA (n = 21)	
d2-Test (%)	53.63 ± 30.00	0.044	38.86 ± 30.58	50 ± 34
CFT[g] (IQS)[e]	103.05 ± 13.73	0.033	95.9 ± 13.73	100 ± 15
FD[j]	101.63 ± 13.55	0.039	94.76 ± 13.99	100 ± 15
	No AW[b] + LDA (n = 104)		AW + LDA (n = 10)	
Arithmetics P[l] (subitem of VIQ)[d]	9.78 ± 2.76	0.002	7.30 ± 1.89	10 ± 3
Picture completion (subitem of PIQ)	9.91 ± 3.25	0.016	7.20 ± 4.26	10 ± 3
	No CALC[c] (n = 45)		CALC (n = 4)	
d2-Test[i] (%)	56.74 ± 30.67	<0.001	13.35 ± 8.42	50 ± 34
RFT[h] (%)	27.05 ± 24.72	<0.001	2.00 ± 2.16	50 ± 34

[a]LDA, low-density area.
[b]AW, any widening (i.e., widening of the sulci or the ventricles).
[c]CALC, calcifications.
[d]PIQ, performance intelligence quotient.
[e]IQS, intelligence quotient scores.
[f]%, percentage score.
[g]CFT, Culture Fair Test.
[h]RFT, Recurring Figures Test.
[i]d2-Test, d2-Concentration Test.
[j]FD, Freedom from distractibility (Calculated Kaufman Factor).
*Significant results are given with *P*-values according to the performed two-sided *t*-test for independent samples. In the right column the mean values of the norm with the standard deviation (±S.D.) of the performed tests are listed.

in the group with abnormal MRI/CCT scans, but this is significant only in the d2-Concentration Test ($P = 0.042$; Table III). However, focusing the interest on the subitems we investigated, we observed a correlation between the appearance of specific morphological alterations and psychological parameters (Table III). Patients with LDA show significantly ($P < 0.05$) lower scores in the CFT, the d2-Concentration Test and the Kaufmann factor ''freedom from distractibility.'' Among patients with LDA combined with any widening of the cerebrospinal fluid spaces, differences were observed in the WISC-R/WAIS-R subitem ''picture completion'' ($P = 0.016$) and in the subitem ''arithmetics'' ($P = 0.002$). The detection of calcifications was significant ($P < 0.001$), correlated with lower scores in the d2-Concentration Test and the Recurring Figures Test in respect of the low number of four patients in the group showing calcifications. The psychological test results were not available in all patients with MRI/CCT scans, and as a result the number of investigated patients in Table III differs from the total of 118. On the other hand, no correlation in view of morphological brain alterations was found in either the neurological examination with the Touwen pattern or the conventional EEG recordings. The comprehensive results of these investigations will be published shortly. Focusing on the sex distribution, we can state that children of both genders are at the same risk of developing CNS abnormalities after irradiation up to 18 Gy. In group A, the male-to-female ratio of abnormal scans was 6/19 (31.6%) vs. 9/20 (45%) and in group B + C 23/39 (59%) vs. 23/40 (57.5%). This was statistically not significant.

DISCUSSION

The results of several studies investigating the CNS of former ALL patients differ widely. For example, no brain damage, especially no white matter changes, was described in the study of Kramer et al. [37], even if patients were irradiated with 18 Gy or 24 Gy, contradictory to the investigation by Peylan-Ramu et al. [11], who reported more than 50% abnormal CCT findings such as white matter changes, widening of the ventricles and

sulci or calcifications in patients receiving ITMTX or intrathecal cytosine arabinosid and cranial irradiation with 24 Gy, comparable with our observations, using CI with 12–18 Gy.

There are four distinct pathological entities that are believed to be the consequences of prophylactic CNS therapy.

Leukoencephalopathy

Leukoencephalopathy is correlated to myelin degeneration [38]. Children who had received cranial irradiation with more than 20 Gy and both ITMTX and systemic methotrexate (> 40 mg/m^2 weekly) treatment are at a greater risk of developing leukoencephalopathy [39]. The clinical symptoms of leukoencephalopathy can be seizures, ataxia, lethargy, slurred speech, spasticity, dysphasia, lowered IQ scores, memory impairments, and confusion. It is reported that these symptoms occurred later than 4 months after irradiation [9]. Possible correlating CCT findings are periventricular hypodensity, dilatation of the ventricles and subarachnoid spaces [40]. The changes can be progressive, but most children survive with signs of permanent neurological deficits, and some recover completely. These serious complications are not found very often under the current treatment methods [41]. We can confirm this observation with our own findings.

The subclinical form of leukoencephalopathy is more common, as the results of Peylan-Ramu et al. [11] have shown, finding CCT abnormalities in 8 (57%) of 14 nonsymptomatic patients who received 24 Gy irradiation and ITMTX. Our own results confirm these investigations (Table II); however, in our study of 79 patients who were irradiated with an age-dependent dose ranging only from 12 to 18 Gy, 46 (58.2%) showed abnormalities in MRI or CCT scans. In 20/79 (25.3%) irradiated patients we saw low-density areas, in contrast to 1/39 (2.6%) patient from group A ($P = 0.002$). Whilst any widening, both widening of the sulci or widening of the ventricles, in combination with low-density areas was not seen in group A, 10/79 (12.7%) of irradiated patients show this abnormality ($P = 0.02$). Therefore, we assume that the lower irradiation doses used in our patient sample may be able to cause brain alterations, especially signs of subacute leukoencephalopathy.

Mineralizing Microangiopathy

This alteration affects the grey matter of the CNS, mainly the region of the basal ganglia, the cerebral cortical sulci and, less frequently, the cerebellar grey matter [42]. Histologically, a deposition of calcium is found in the small blood vessels, with a particular occlusion of the lumens by precipitated mineralized debris. This is accompanied by a dystrophic calcification in the surrounding neural tissue. The prophylactic irradiation of the brain is assumed to be the main cause in developing these changes. Namely, patients who were younger than 10 at the time of irradiation, a dose higher than 15 Gy, a post-irradiation interval of more than 10 months and multiple CNS leukemic relapses with more intensive therapy, are further variables of risk for mineralizing microangiopathy [43]. Other investigators believe that additional doses of methotrexate and cytosine arabinosid may influence the progression of these lesions [44]. Possible clinical manifestations of these alterations are headaches, seizures, EEG abnormalities, dyscoordination, gait abnormalities, memory deficits, learning disorders, declines in IQ scores, and various behavioral difficulties [9,41]. These findings appear with a latency of about 10 months up to several years after the irradiation. The calcifications can be detected more clearly using CCT scans than MRI scans, mainly in the region of the basal ganglia or in the grey matter of the cortex. The more chronic form of mineralizing microangiopathy occurs only if a combination of both CI and ITMTX is used. In our study population, only a reduced number of patients (n = 49) received CCT scans, because many parents refused the irradiation using CCT and agreed to MRI scans. In this group of patients receiving CCT scans, 4/49 had detectable calcifications (8.2%). However, all calcifications were detected in group B and C (4/31 [12.9%]), whereas no calcification was seen in group A (Table II). One reason for this low incidence of calcifications could be the relatively low dose of irradiation used (12–18 Gy). However, it is significant that three of four patients belonged to group B ($P = 0.027$), i.e., the group with the ITMTX dosages before CI but with the highest cumulative dose in ITMTX and the highest number of dosages. Therefore, a higher ITMTX dose in combination with cranial irradiation may cause a higher risk for calcifications. Similar results are reported in a review by Ochs et al. [45], who listed the frequency of anatomical abnormalities of the brain in relation to type of CNS prophylaxis and found that a chemoprophylaxis alone, as in our group A, causes no brain calcifications in contrast to the irradiated patients (18 Gy) which present up to 7.2% calcifications, as in our groups B and C. Another explanation for these findings could be the additional therapy using SMHDMTX in group B in contrast to group C. But cranial irradiation appeared to be the main risk factor. These findings confirm the review of Bleyer et al. [41] who described this alteration as usually seen after combined chemotherapy and CI.

Subacute Necrotising Leukomyelopathy

Patients receiving cranial or cranial-spinal irradiation followed by ITMTX applications displayed alteration of the spinal cord in the investigations conducted by Price [46]. These patients presented a focal myelin necrosis in the posterior and/or lateral columns of the spinal cord, extensive cervical and lumbar, milder in the thoracic section. He hypothesised that a folate deficiency resulting

from the ITMTX treatment with cumulative doses > 200 mg and a treatment duration longer than 2 years may be the cause. This injury of spinal cord radiation is related to neurological findings to the cord level of the radiation field [47]. Serious neurological impairments as clinical signs for leukomyelopathy were not found in our patient sample.

Brain Tumors

Previous investigations [48, 49] and investigations by Gutjahr et al. [50] and Kaatsch et al. [51] show that former ALL patients with prophylactic CI who were younger than 5 years at the time of treatment are at a risk of 1.5–3% to develop secondary malignancies within the first 10 years after therapy. Their secondary malignancy is, in 21.7–30% of cases, a brain tumor. In our study population there was no case of secondary malignancy, because this was an exclusion criteria.

We can state that the serious impairments described above which can be caused by therapy were not observed amongst our study group. One reason could be the comparatively mild prophylactic therapy of our patients in contrast to the published data, because we included neither relapsed patients nor children of the high-risk branches. The highest cumulative doses used in our subjects for irradiation were 18 Gy, for ITMTX 168 mg and for SMHDMTX 2,000 mg/m^2. Most studies enrolled patients with 20 Gy or more for CNS prophylaxis and did not compare patient groups with and without CI [9].

The appearance of neuroradiologically detectable alterations in our study was significantly connected with prophylactic CI. Group C with ITMTX during and after CI showed more brain alterations than group B with CI after chemotherapy, although there are no significant differences between these groups in our analysis. Not only the incidence of MRI/CCT findings increased in the CI groups, but also the number of alterations per patient was significantly greater in the irradiated groups. Our results lead to the conclusion that CI seemed to be the worst factor causing CNS changes. However, MTX therapy in combination with CI, especially given after CI, may also further increase the risk for some alterations. We can confirm the findings of Bleyer et al. [41] that MTX therapy without CI is the safest therapeutic option with regard to the risk of brain damage. The combination of WS and/or WV and LDA, which can be interpreted as both a sign of leukoencephalopathy or of brain atrophy [40], was not perceived in group A, but in 12.7% in group B + C (Table II, Fig. 2). We suggest the combination of CI and ITMTX and SMHDMTX or ITMTX during and after CI as a main factor for causing these significant alterations. The fact that WS and/or WV without LDA is distributed almost equally in all three groups (Table II) allows the interpretation that the influence of the systemic and intrathecal MTX treatment alone are more likely to cause any type of brain atrophy, and, in combination with CI, as described above, additional white matter necrosis detected as LDA [52]. In our results, these changes are significantly correlated with lower scores in the subitems ''arithmetics'' and ''object completion'' of the Wechsler scales. Mineralizing microangiopathy, defined as calcifications, were detected only in the irradiated groups B and C, confirming the findings of Price [43]. Our finding that patients with cerebral calcifications score significantly lower in both the d2-Concentration-Test and the Recurring Figures Test are comparable with the results published by Brouwers et al. [53,54] who described a decrease of memory functions by patients with abnormal CCT scans, especially calcifications. However, their patients were irradiated with 24 Gy. This can be seen in the correlation of cerebral calcifications and loss of both power of concentration and memory functioning, but this conclusion must be judged carefully because the total number of obtained CCT scans was only 49.

The higher appearance of pathological MRI/CCT scans in the irradiated (Fig. 5) after a post-therapeutic interval longer than 7 years may explain the neuropsychological results of Jankovic et al. [55], who described a significant decline in full scale intelligence quotient in the irradiated group after lengthening the time from diagnosis.

The age-related distribution of brain atrophy and leukoencephalopathy shows that brain atrophy is more rare in the younger patients under age 4 years, and leukoencephalopathy is frequent between ages 2 to 5 (Fig. 4). Carli et al. [17] reported a study with 72 successfully treated patients, in which an age at diagnosis under 5 was found to be the most important risk factor for developing CT scan abnormalities. This may be right, but when we look at our results, we found that we must differentiate between irradiated children under 2 and 2 to 5 years at diagnosis. All those are under 5 and show low-density areas in 16/48 (33.3%) (i.e., 23.5% of all patients under age 5). But the under 2 years age group shows low-density areas only in 1/10 (10%) of the irradiated patients, whereas the 2 to 5 group presents low-density areas in 15/38 (39.5%) of the irradiated cases (i.e., 26.8% of all patients of this group) (Figs. 3, 4). Our observation that the prevalence of abnormal MRI/CCT scans in the irradiated groups is the lowest when the children are under age 2 at time of diagnosis (Fig. 3), can perhaps be explained by recent studies of brain development. These studies were able to show that the neuronal development follows distinct stages, which are characterised through a dramatic increase in synaptogenesis within the first 24 months [56,57]. Our observations may be a sign for the enhanced neuronal resistance of children younger than 2 years at the beginning of the treatment and their ability to correct the brain damage caused by CNS prophylaxis

than children who were older. In this group, the irradiation dose did not differ from those who were older (15.9 Gy vs. 17.3 Gy in mean) so that a possible lower irradiation dose in the younger age groups can not be the reason for this observation, but there are only 10/79 irradiated patients younger than 2. This age-dependent prevalence was first observed in the EEG analysis [61], thus confirming the hypothesis of the enhanced neuronal resistance within the first 24 months of life against the described therapy modalities.

In contrast to reports which describe in neuropsychological investigations a lower scoring in IQ tests in girls than in boys [62,63], we found no morphological impairments which are related to sex neither in the irradiated or in the nonirradiated group.

The distribution of the two medium-risk treatment branches (BFM-81/MR and BFM-83/MR) in the irradiated groups (groups B and C) may suggest that the greater number of MRI/CCT findings in these groups is founded on the more severe disease, but the number of abnormal MRI/CCT findings was not significantly higher in the MR branches (15/28; 53.6%) than in the SR/LR branches (46/90; 51.1%; $P = 0.82$).

Conclusion

We conclude that children receiving CI in a low doses between 12 and 18 Gy in combination with SMHDMTX and/or ITMTX are at a greater risk of developing brain damage than patients without irradiation. In addition, the number of alterations is higher in the group with CI. Nevertheless, CNS prophylaxis without CI can also cause brain alterations, especially widening of the sulci or ventricles as a sign for brain atrophy. The combination of both CI and ITMTX appears to exert the worst impact on morphological brain alterations. The finding of low-density areas, in combination with widening of the sulci/ventricles as possible signs of subacute leukoencephalopathy, are correlated with lower scoring in the Wechsler scales subitems ''arithmetics'' and ''picture completion.'' In our study, patients with calcifications are at a higher risk of showing a loss of power in concentration and in memory functioning, as the results of the d2-Concentration Test and the Recurring Figures Test have shown, in regard to the small number of four patients with detectable calcifications.

The number of alterations in the irradiated groups reaches, with a longer post-therapeutic interval, a higher level than in the nonirradiated group. The low prevalence of receiving neuroradiological alterations within a small group of 10 irradiated children who were younger than 2 years at diagnosis may reflect the ability of the young brain to possibly correct damages caused by an irradiation dose maximum up to 18 Gy. Sex has no influence on the risk of developing CNS impairments in both groups, irradiated and nonirradiated. The results of the neurological and neurophysiological investigations will be published separately [58,59,60].

Our results show that there is a necessity to carry out prospective studies in the future, to have a ''status quo'' at the beginning of the disease and over the time, to elucidate the onset and change of CNS impairments.

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APPENDIX

The following institutions and investigators participate in the CNS Late Effects Working Group: University of Berlin: G. Henze, U. Brandl, K. Berger-Jones, S. Wiesnewski; University of Bonn: U. Bode, C. Hasan, M. Kusch; University of Düsseldorf: U. Göbel, G. Janßen, U. Kischlat-Steger, G. Steegmanns; University of Erlangen: J.D. Beck, W.J. Huk, M.A. Überall, W. Meier, H. Hertzberg; University of Freiburg: M. Brandis, R. Korinthenberg, C. Niemeyer, Fr. Olschewski; University of Gießen: F. Lampert, G. Neuhäuser, U. Tolks-Brandau; University of Graz: Ch. Urban, H. Lackner; University of Jena: F. Zintl, D. Fuchs, G. Skirl, E. Ruppert; University of Mainz: J. Michaelis, P. Kaatsch; University of München: C. Bender-Götze, T. Rauch; University of Tübingen: D. Niethammer, R. Dopfer, S. Kochendörfer; University of Würzburg: J. Kühl, H. Ottensmeier.

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